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EXAMINER	
SWITZER, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,968	GERMINO ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,16-25,28-37,39-42,44,46-52,55-61 and 76-78* is/are pending in the application.

4a) Of the above claim(s) *30 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7, 16-25, 28-29, 31-37, 39-42, 44, 46-52, 55-57, 29-61, and 76-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner handling this application has changed. Please address future correspondence to Juliet Switzer, Art Unit 1634.

2. This action is written in response to applicant's correspondence submitted 3/22/06. Claims 1, 20, 25, 44, 59, and 60 have been amended, claims 5-6, 8-15, 26-27, 38, 43, 45, 53-54, and 62-75 have been canceled, and claims 76-78 have been added. Claims 1-4, 7, 16-25, 28-37, 39-42, 44, 46-52, 55-61, and 76-78 are pending. Claims 30 and 58 are withdrawn from prosecution, and the remaining claims are examined in this office action. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive to place the application in condition for allowance for the reasons that follow. Any rejections not reiterated in this action have been withdrawn.

Election/Restrictions

3. The first action on the merits in this application was written to address methods and products insofar as they relate to the primer pair of SEQ ID NO: 3 and 4 and the nested primer pair SEQ ID NO: 19 and 20. Further, the mutation elected for prosecution is the mutation at position 3336 of SEQ ID NO: 1, wherein the nucleotide at position 3336 is deleted (see office action mailed 1/29/04, page 2). The interview summary on 10/20/04 the examiners suggested requiring all 8 of the primer pairs in the independent claim, referring, it appears to a possible claim which requires a primer pair for the amplification of each "section" that was present in claim 5 of the claim set filed 6/10/04. Applicant's instant claims set forth in the alternative eight different primers. Where there are alternative SEQ ID NO given in a claim, the claim has been

considered only insofar as it relates to the ELECTED SEQ ID NO. For example, independent claim 1 requires two primers selected from the group consisting of SEQ ID NO: 3, 4, 5, and 6, and two primers selected from the group consisting of SEQ ID NO: 19, 20, 21, and 22. This claim has been examined to consider the primers for the first amplification product to be SEQ ID NO: 3 and 4, and the primers for the second amplification product to be SEQ ID NO: 19 and 20, as set forth by the election. Likewise, claim 25 has been examined insofar as the "set of primer pairs" is selected from the group consisting of SEQ ID NO: 3, 4, 19, and 20, again consonant with the election, thus, since a "set of primer pairs" requires at least four primers, the claim has been examined insofar is it requires the four elected primers. Claims 44 and 60 have been treated like claim 1, as they recites the primers for the method in a similar fashion.

4. Applicant is advised that should claim 1 be found allowable, claim 7 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Likewise, Applicant is advised that should claim 16 be found allowable, claim 17 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Given that claim 1 now requires that the set of eight primer pairs hybridize to flanking regions of each of the recited regions, it does not appear that claim 7 further limits claim 1 or that claim 17 further limits claim 16.

5. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the specification does not provide antecedent basis for a deletion in SEQ ID NO: 1 at position 3336. The specification at page 109 discusses a deletion referred to at G3336 in exon 13, but does not ever discuss a deletion any mutation or deletion within exon 1 or the surrounding introns, especially not the deletion at position 3336 of SEQ ID NO: 1 that is set forth in claim 20.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 7, and 17-19 are indefinite because the claim appears to require that the eight primers "selectively hybridize to a flanking sequence...of each of polycystic kidney disease-associated protein-1 (PDK1) gene sequences" and it is not clear if each of the eight primers must all hybridize to each of the eight flanking regions, or if the claim intends to set forth that the set includes at least one primer that flanks each of the regions, or some other interpretation.

Claim 7 is indefinite over the recitation "comprising a primer of claim 1" since claim 1 requires at least eight primers, and not a single primer, it is confusing what "a primer of claim 1"

refers to, whether it is intended to refer to any one primer in the set required in claim 1 or whether the claim intends to refer to the entire set of primers.

Claims 20-24 are indefinite over the recitation "wherein the nucleotide sequence corresponds to nucleotide 3336 of SEQ ID NO: 1, and wherein nucleotide 3336 is deleted" because "the nucleotide sequence" refers to the previous part of the claim which sets forth "a contiguous sequence of at least ten nucleotides substantially identical to a nucleotide sequence of SEQ ID NO: 1," and it is not clear what it means for this ten nucleotide sequence to "correspond" to a particular position of SEQ ID NO: 1, especially given that the claim continues by requiring that this single corresponding nucleotide is deleted. Furthermore, it is not clear what it means to require within the broadly defined ten nucleotide sequence that nucleotide "3336" is deleted. Nucleotide 3336 of SEQ ID NO: 1 is a "t", does requirement mean that there can be no "t" nucleotide in the claimed sequence. Since the claim does not clearly set forth any context within which the deletion must take place, it is indefinite as to how to identify a molecule that has the requisite deletion.

Claims 25, 28, 29, 31-37, 39-42, and 76 are indefinite over the recitation "said conditions" in the final line of the "contacting" step of claim 25 because this phrase lacks proper antecedent basis in the claim and it is therefore not clear which conditions are "said conditions."

Claims 55, 56, and 57 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete because they depend directly or indirectly from a canceled base claim. See MPEP 608.01(n)[R-3](V). These claims were not treated in view of the prior art because they are incomplete.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7, 16-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the limitation of "A set of primers, comprising at least 8 primers" in claim 1 appears to represent new matter. When this limitation was first added to the claim in the papers received 8/19/05, no specific basis for this limitation was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. The examiner identified discussion of a set of eight primer pairs (which would comprise 16 primers) at page 22 (¶0045) of the specification, but no basis for a set comprising at least eight primers could be identified. Since no basis has been identified, the claims are rejected as incorporating new matter.

In claim 25, the language of the claim suggests that all of the primer pairs selected from the elected primer pairs of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 19, and SEQ ID NO: 20 would "selectively hybridize to a PKD1 polynucleotide comprising SEQ ID NO: 1 and amplify a region of the PKD1 polynucleotide but not a PKD1 polynucleotide homolog," but the teachings of the specification provide that only SEQ ID NO: 3 has this ability. The other primers in the elected are not disclosed as having this specificity (see Examples). Therefore, the recitation that

they do have this specificity is new matter. Claim 44 has a similar problem because it also sets forth that the primer pairs have this function, and so claim 44 and the claims that depend from it are also rejected for new matter.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 20, 21, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Gonczol et al. (WO 97/40165).

Gonczol et al. teach an isolated nucleic acid which comprises the nucleotide sequence 5'-AGCGCGCCGGG-3' contained within the nucleic acid encoding human CMB phosphoprotein (pp) 150 (see nucleotides 3290-3300 and 5688-5698 of the sequence given in Figure 6A and B; also see figure description, p. 4). This eleven nucleotide sequences is complementary to nucleotides 3631-3642 of instant SEQ ID NO: 1, except that the "T" at position 3336 is deleted. Thus, Gonczol et al. teach an isolated polynucleotide comprising a sequence complementary to at least ten nucleotides "substantially identical" to a nucleotide sequence of SEQ ID NO: 1, wherein the nucleotide sequence "corresponds" to nucleotide 3336 and wherein nucleotide 3336 is deleted. Gonczol et al. teach vectors and host cells comprising this sequence (p. 10, first full ¶, for example). Thus, Gonczol et al. provide nucleic acids and constructs which meet the limitations of claim 20, 21, and 22.

11. Claims 20, 23, and 24 rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US 5474796).

Brennan provide an array, which is a solid matrix, having thereupon every possible 10-mer nucleic acid in a separate position on the array. Thus, Brennan provides each possible isolated polynucleotide of ten nucleotides in length, including any that are within the scope of instant claim 20. With regard to claim 23, these nucleic acids are all immobilized on a solid matrix, and with regard to claim 24, there are a plurality of nucleic acids on the solid matrix which meet the limitations of claim 20.

12. Claims 20, 23, and 24 rejected under 35 U.S.C. 102(b) as being anticipated by Chee et al. (US 5837832).

Chee et al. provide an array, which is a solid matrix, having thereupon a variety of nucleic acids, one of which is their SEQ ID NO: 183. This sequence shares 90% identity with nucleotides 3329- 3339 of instant SEQ ID NO: 1, wherein the "T" at position 3336 is deleted. nucleotides 3631-3642 of instant SEQ ID NO: 1, except that the "T" at position 3336 is deleted. Thus, Chee et al. teach an isolated polynucleotide comprising a sequence complementary to at least ten nucleotides "substantially identical" to a nucleotide sequence of SEQ ID NO: 1, wherein the nucleotide sequence "corresponds" to nucleotide 3336 and wherein nucleotide 3336 is deleted. With regard to claim 23, these nucleic acids are all immobilized on a solid matrix, and with regard to claim 24, there are a plurality of nucleic acids on the solid matrix, one of which is their SEQ ID NO: 183 (see Col. 14-16).

Claim Rejections - 35 USC § 112

13. Claims 1-4, 7, and 16-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Independent claim 1 is drawn to a set of primers which comprises at least 8 primers that selectively hybridize under highly stringent conditions to a nucleotide sequence which flanks a series of portions of instant SEQ ID NO: 1, which is the human polycystic kidney disease-associated protein gene sequence. The claim requires that the primers comprise a 5' region which can hybridize to both PKD1 and "a PKD1 gene homolog" and a 3' region that selectively hybridizes to a PKD1 gene sequence but not to the gene homolog. Instant claim 1, as elected, requires instant SEQ ID NO: 3, 4, 19, and 20. Of these, only instant SEQ ID NO: 3 is identified in the specification as being a "PKD1 specific primer" (see Table 1, p. 103 of the specification). The specification identifies eight additional primers as being PKD1 specific, that is instant SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18. The scope of the claim is very broad with regard to the identity of the required eight primers that are contain portions that hybridize to PKD1 but not to PKD1 homologues, since of these 8 only one is identified by the recited SEQ ID NO: 1. These primers can possibly be chosen from anywhere within the disclosed 53,522 nucleotide sequence of instant SEQ ID NO: 1, but there is no guidance as to which regions are unique to PKD1 relative to the undefined homologs.

The specification provides an over five kilobase nucleic acid sequence (instant SEQ ID NO: 1) which it teaches is a "wild-type" PKD1 gene sequence (¶0054). The specification does not provide the nucleic acid sequence of any "PKD1 gene homolog" nor does the specification provide a definition of what structural features identify such a homolog. The specification teaches that the sequence of PKD1 was aligned with that of two homologues present in GenBank record AC002039 (¶0223). This record does not annotate the presence of the homologues. The identity of the nucleic acid sequence of PKD1 homologues is essential for the practice of the claimed invention, as one would need the nucleic acid sequence of these homologues to in order to select additional members of the claimed set of oligonucleotide primers. Roelfsema et al. teach a model of repeated structure of PKD1 gene on chromosome 16, teaching a repetition iteration of at least six times, and states that the precise number of repetitions is unknown (1997, as cited in IDS, see Figure legend). In addition, the post-filing date art teaches that there are at least four additional homolog sequences of PKD1 on human chromosome 16p13.1, all with a high degree of identity to SEQ ID NO: 1, and that the exact number of the homologous genes as well as their structure is yet unknown (Bogdanova et al. Genomics, 2001, see first page and throughout). Bogdanova et al. continues by stating "the accumulation of precise sequence information on the HG is desperately required to design PKD1-specific reagents that would serve more conventional scanning techniques (p. 334, first column). Thus, the claims encompass primers which are designed to exclude the amplification of nucleic acid homolog sequences that were not described at the time the invention was made, and that are not described in the instant specification. There is no guidance in the specification as to how to look at instant SEQ ID NO: 1 and to select, of all of the possible primers (millions of possible primers within SEQ ID NO: 1)

which ones would meet the functional requirements set forth by the claims, and thus could be included within the set of "at least 8" claimed primers.

14. Claims 20-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are drawn to isolated polynucleotides and constructs comprising polynucleotides, wherein the polynucleotide comprises a contiguous sequence of at least ten nucleotides "substantially identical" to a nucleotide sequence of SEQ ID NO: 1 or to "a nucleotide sequence complementary thereto." The claims further require that the nucleotide sequence "corresponds to nucleotide 3336 of SEQ ID NO: 1, and wherein nucleotide 3336 is deleted." The final recitation of the claim is indefinite, but it appears that applicant may be trying to claim a fragment of SEQ ID NO: 1 wherein position 3336 has been deleted. The claim language is extremely broad. The claim requires that the claimed polynucleotide comprises at least ten nucleotides that are "substantially identical" to a portion of SEQ ID NO: 1. The phrase "substantially identical" is sufficiently broad so as to encompass a nucleotide sequence with any level of "substantial identity" to a ten nucleotide fragment of SEQ ID NO: 1, since "substantial" is not provided a limiting definition in the specification, it is broadly interpreted to include any level of identity, since one or two of ten nucleotides is substantial. Further, the claim recited that the polynucleotide can comprise nucleotide sequence complementary to the broadly defined

"substantially identical" ten nucleotides, without defining an level of complementarity required. Thus, the claim encompasses a polynucleotide with any level of complementarity to a substantially identical ten nucleotide fragment of SEQ ID NO: 1, wherein nucleotide 3336 (which is a T) is deleted. And the claims are broadly drawn using the claim language "comprising" which means that this broadly set forth ten nucleotide structure can be contained within any possible sequence context of any length. Thus, the claims are extremely broad in nature and encompass polynucleotides of millions of possible origins and identities, including genes and gene fragments that have very little structural and no functional relationship to instant SEQ ID NO: 1. The specification describes instant SEQ ID NO: 1, and therefore fragments consisting of instant SEQ ID NO: 1 are described. The specification further teaches a deletion of a single nucleotide from position 3336 of SEQ ID NO: 1 (pertaining to the elected invention), so nucleotide fragments that consist of fragments of instant SEQ ID NO: 1 except that the nucleotide at position 3336 is deleted are also described. However, given the limited disclosure of the specification and given the extremely broad nature of the claimed invention, it is concluded that the claimed invention is not supported with proper written description.

15. Claims 1-4, 7, 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for primers having SEQ ID NO: 3, 5, 8, 10, 11, 14, 16, and 17, which can be used to specifically amplify PKD1 gene having SEQ ID NO: 1 and no PKD1 gene homologs, does not reasonably provide enablement for additional primers that have this property. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

16. Claims 20-24, 28-37, 39-42, 44, 46-52, 55-61, and 76-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

Independent claim 1 is drawn to a set of primers which comprises at least 8 primers that selectively hybridize under highly stringent conditions to a nucleotide sequence which flanks a series of portions of instant SEQ ID NO: 1, which is the human polycystic kidney disease-associated protein gene sequence. The claim requires that the primers comprise a 5' region which can hybridize to PKD1 and optionally "a PKD1 gene homolog" and a 3' region that selectively hybridizes to a PKD1 gene sequence but not to the gene homolog. Instant claim 1, as elected, requires instant SEQ ID NO: 3, 4, 19, and 20. Of these, only instant SEQ ID NO: 3 is identified in the specification as being a "PKD1 specific primer" (see Table 1, p. 103 of the specification). The specification identifies eight additional primers as being PKD1 specific, that is instant SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18. The scope of the claim is very broad with regard to the identity of the required eight primers that are contain portions that hybridize to PKD1 but not to PKD1 homologues, since of these 8 only one is identified by the recited SEQ ID NO: 1. These primers can possibly be chosen from anywhere within the disclosed 53,522 nucleotide sequence of instant SEQ ID NO: 1, but there is no guidance as to which regions are unique to PKD1

relative to the undefined homologs. Further, the specification does not provide any clear definition of how much sequence difference is necessary between two molecules for one to be a "homolog" of the other, as opposed to one being a polymorphic variant of the other. Thus, for these product claims the nature of the invention depends on the ability to identify primers which meet the functional characteristics set forth in the claims.

Independent claim 20 and the claims that depend from claim 20 are drawn to isolated polynucleotides and constructs comprising polynucleotides, wherein the polynucleotide comprises a contiguous sequence of at least ten nucleotides "substantially identical" to a nucleotide sequence of SEQ ID NO: 1 or to "a nucleotide sequence complementary thereto." The claims further require that the nucleotide sequence "corresponds to nucleotide 3336 of SEQ ID NO: 1, and wherein nucleotide 3336 is deleted." The final recitation of the claim is indefinite, but it appears that applicant may be trying to claim a fragment of SEQ ID NO: 1 wherein position 3336 has been deleted. The claim language is extremely broad. The claim requires that the claimed polynucleotide comprises at least ten nucleotides that are "substantially identical" to a portion of SEQ ID NO: 1. The phrase "substantially identical" is sufficiently broad so as to encompass a nucleotide sequence with any level of "substantial identity" to a ten nucleotide fragment of SEQ ID NO: 1, since "substantial" is not provided a limiting definition in the specification, it is broadly interpreted to include any level of identity, since one or two of ten nucleotides is substantial. Further, the claim recited that the polynucleotide can comprise nucleotide sequence complementary to the broadly defined "substantially identical" ten nucleotides, without defining an level of complementarity required. Thus, the claim encompasses a polynucleotide with any level of complementarity to a substantially identical ten

nucleotide fragment of SEQ ID NO: 1, wherein nucleotide 3336 (which is a T) is deleted. And the claims are broadly drawn using the claim language "comprising" which means that this broadly set forth ten nucleotide structure can be contained within any possible sequence context of any length. Thus, the claims are extremely broad in nature and encompass polynucleotides of millions of possible origins and identities, including genes and gene fragments that have very little structural and no functional relationship to instant SEQ ID NO: 1. Thus, the nature of the invention in this case, first involves the ability to synthesize the claimed molecules, but second requires a knowledge of how to use those molecules.

The remaining claims are method claims, and recite amplification steps which eventually lead to "identifying the presence or absence of a mutation in the PKD1-specific amplification product, thereby detecting the presence or absence of a mutation in the PKD1 polynucleotide in the sample," with claim 44 and 60 reciting that the mutation identifies subjects at risk for a PKD1 associated disorder or diagnoses such a disorder in a subject. The claims encompass the identification of a mutation at any position within the amplified products, which given the elected primer sequences encompass possible mutations at 2300 possible nucleotides. Regarding claims 25 and those that depend from them, these claims do not recite an association with a disease, but in the nature of the method requires such a knowledge in order for the method to be "used." While one could practice the method, at least with regard to the single disclosed mutation in this amplification product, one would not know how to "use" the method as the specification does not set forth the relationship between the deletion at nucleotide 3336 and any "PKD1 related disorder. The scope of these claims is also quite broad with regard a "PKD1 related disorder," encompassing disorders such as ADPKD or acquired cystic disease, as

mentioned by the specification, but also any disease or disorder that has symptoms in common with these diseases, such as urinary tract infections, blood in the urine, liver and pancreatic systs, and kidney stones.

Teachings in the specification and the prior art

The specification provides an over five kilobase nucleic acid sequence (instant SEQ ID NO: 1) which it teaches is a "wild-type" PKD1 gene sequence (¶0054). The specification does not provide the nucleic acid sequence of any "PKD1 gene homolog" nor does the specification provide a definition of what structural features identify such a homolog. The specification teaches that the sequence of PKD1 was aligned with that of two homologues present in GenBank record AC002039 (¶0223). This record does not annotate the presence of the homologues, nor is any other guidance or source given in the specification or the prior art as to how the location of these "homologs" within prior art sequences. The identity of the nucleic acid sequence of PKD1 homologues is essential for the practice of the claimed invention, as one would need the nucleic acid sequence of these homologues to in order to select additional members of the claimed set of oligonucleotide primers. Roelfsema et al. teach a model of repeated structure of PKD1 gene on chromosome 16, teaching a repetition iteration of at least six times, and states that the precise number of repetitions is unknown (1997, as cited in IDS, see Figure legend). The art teaches that there are at least four additional homolog sequences of PKD1 on human chromosome 16p13.1, all with a high degree of identity to SEQ ID NO: 1, and that the exact number of the homologous genes as well as their structure is yet unknown (Bogdanova et al. Genomics, 2001, see first page and throughout). Bogdanova et al. continues by stating "the accumulation of precise sequence

information on the HG is desperately required to design PKD1-specific reagents that would serve more conventional scanning techniques (p. 334, first column). Further, Phakdeekitcharoen et al. discuss the problem with selecting specific primers for the PKD1 gene, teaching that the PKD1 gene has several relevant features that make it difficult to study the PKD1 gene using molecular biology techniques, including high GC content, the lengthy coding sequence, the presence of homologs with high sequence identity and the presence of an unusual element within the gene that includes a high degree of polypyrimidines. The art recognizes that working with this gene is highly unpredictable. In such a highly unpredictable setting, a high degree of guidance is required to practice the claimed invention. Thus, the claims encompass primers which are designed to exclude the amplification of nucleic acid homolog sequences that were not described at the time the invention was made, and that are not described in the instant specification. There is no guidance in the specification as to how to look at instant SEQ ID NO: 1 and to select, of all of the possible primers (millions of possible primers within SEQ ID NO: 1) which ones would meet the functional requirements set forth by the claims, and thus could be included within the set of "at least 8" claimed primers.

Regarding claim 20, The specification describes instant SEQ ID NO: 1, and therefore fragments consisting of instant SEQ ID NO: 1 are described. The specification further teaches a deletion of a single nucleotide from position 3336 of SEQ ID NO: 1 (pertaining to the elected invention), so nucleotide fragments that consist of fragments of instant SEQ ID NO: 1 except that the nucleotide at position 3336 is deleted are also described. However, given the limited disclosure of the specification and given the extremely broad nature of the claimed invention, it is concluded that the claimed invention is not supported with proper written description.

The specification does not provide any discussion about a mutation at position 3336 of instant SEQ ID NO: 1. This mutation would be within the exon 1 or the surrounding introns, and the specification does not make any mention of such a mutation. The specification does not provide any data which suggests a relationship between this mutation and any possible PKD1 related disease or disorder. Regarding the method claims, the specification does teach and exemplify that it is unpredictable whether mutations or polymorphisms in the PKD1 gene will be associated with disease, specifically teaching in ¶ 0054 that not all nucleotide variations in SEQ ID NO: 1 will correlate with the signs and symptoms characteristic of a PKD1 associated disorder, and indeed the specification exemplifies in Table 2 that some mutations discovered segregate with disease and some do not. Thus, of all of the possible mutations that might be identified within the regions amplified in the rejected method claims, it is highly unpredictable which ones will be associated with disease. The specification has not provided a single mutation within this region that appears to be prognostic of, let alone diagnostic of disease. It is highly unpredictable whether or not such a mutation exists in this amplified region, and it is highly unpredictable whether one could identify such a mutation.

Quantity of experimentation

The quantity of experimentation required to practice the claimed invention, given the high degree of unpredictability in this art area is enormous. For the claims drawn to primer pairs, in order to practice the invention, one would have to undertake substantial trial and error experimentation to determine which possible primers, other than those comprising the SEQ ID NO: specifically given in the specification, would meet the functional requirements set forth in the claims. This would involve the synthesis of primers, but also extensive experimentation to

determine if the synthesized primers are specific to PKD1 and not to PKD1 homologs. Given the fact that there is no clear disclosure of what structural features define the PKD1 homologs in the specification, nor any requirement which indicates how much sequences have to differ from instant SEQ ID NO: 1 to be considered a homolog, and the disclosure in the prior and post filing date art that there are at least six different homologs but maybe more which are unidentified, this work would require extensive experimentation. For claims 20-24, the use of the claimed invention would require extensive and entirely unpredictable work to determine if an association exists between the deletion at position 3336 of SEQ ID NO: 1 and any relevant phenotype, though the claims do not require such a use, the use of a molecule which comprises this deletion would require such knowledge. Regarding the method claims, one would have to undertake extensive studies to first identify potential mutations or polymorphisms within the amplified region, other than the single disclosed example. Whether or not such polymorphisms or mutations exist is itself highly unpredictable, and if they do exist, the location and structure of these variants is highly unpredictable. Once mutations are identified, one would have to undergo further case controlled studies in patient and control populations to determine if the variants are predictive of any disease phenotype, and if so, which of the possible "PKD1 associated disorders" are predicted by the newly discovered mutation.

Conclusion

Thus, having carefully considered each of these factors, it is concluded that it would require undue experimentation to make and use the claimed invention commensurate in scope with claims 1-4, 7, and 16-19, and to make and use the remainder of the rejected claims.

Conclusion

Conclusion

17. Claims 1-4, 7, 16-19, 25, 28-37, 39-42, 44, 46-52, 58-61, and 76-78 are free of the prior art. These claims have all been examined as if they require the originally elected primer pairs, SEQ ID NO: 3 and 4 and SEQ ID NO: 19 and 20. Insofar as each of these claims requires the use of SEQ ID NO: 3, the claims are free of the prior art. The closest prior art, exemplified by previously cited Klinger et al. (US 5654170) provides the sequence of the full length PKD1 gene, which comprises instant SEQ ID NO: 3. Klinger et al. also generically teach the selection of oligonucleotides that discriminate the PKD1 gene from PKD1 homologues (see their Col. 5, lines 40-55). Klinger et al. do not provide any specific guidance as to which portions of their SEQ ID NO: 1 would be relevant for selecting polynucleotides with these discriminatory features, nor do Klinger et al. provide the sequence of any PKD1 homologues. The instant specification demonstrates that SEQ ID NO: 3 does in fact provide this specificity (see Example 1). Thus, methods and products which require a primer consisting of instant SEQ ID NO: 3 are free of the prior art.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this

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